Fachkurs - FBA

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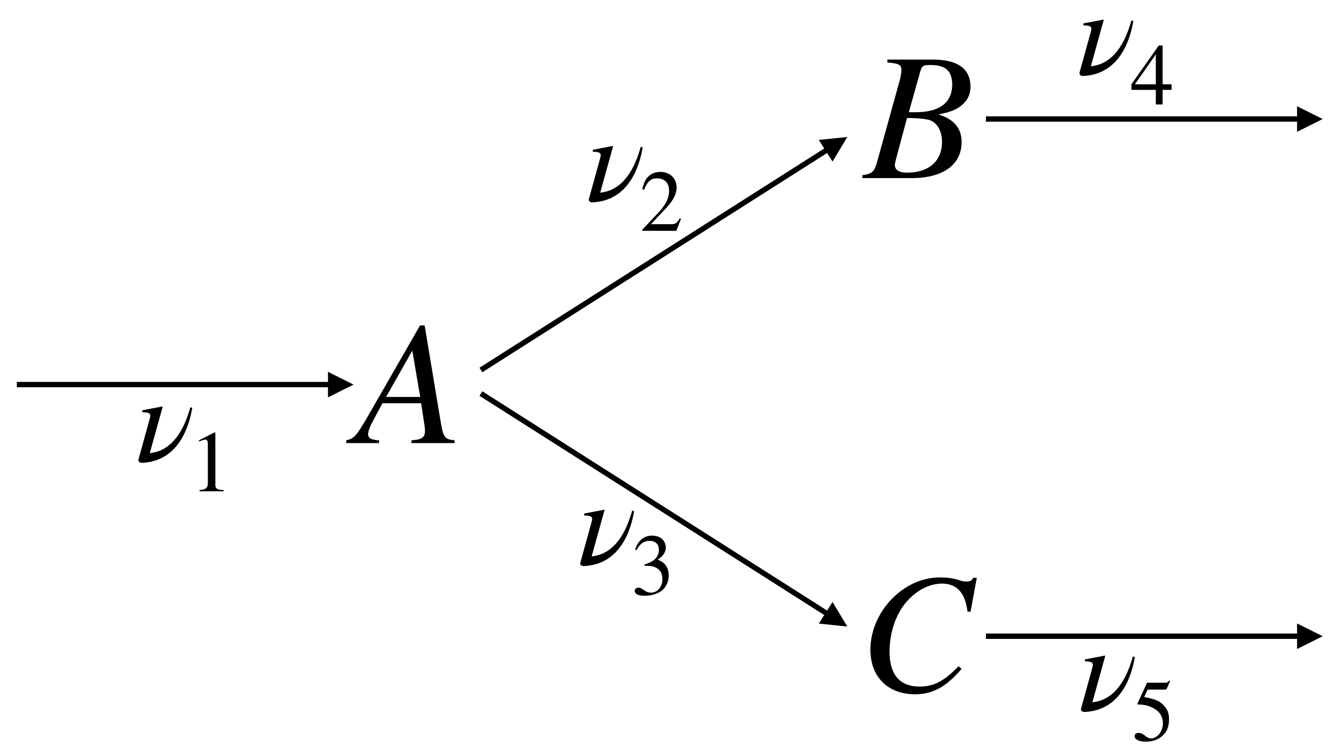
Seminar 01.06.2023
TBP

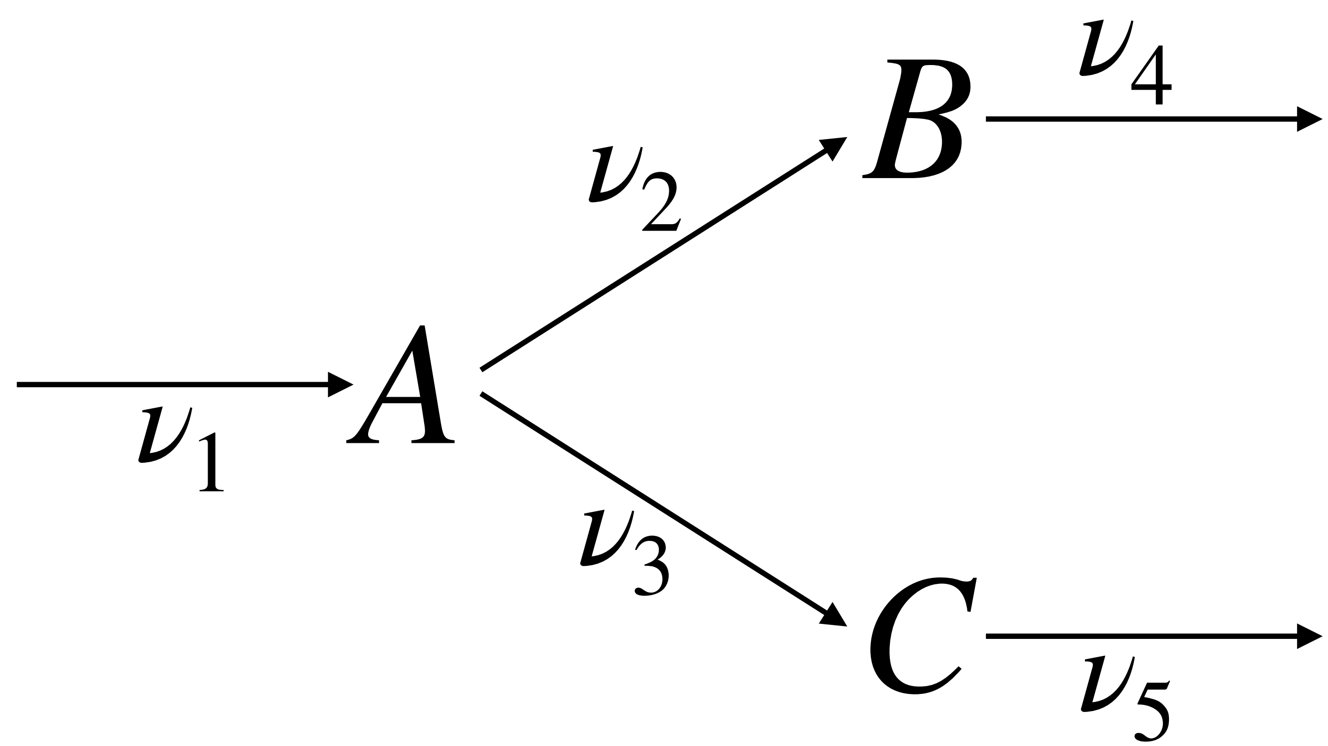
Outline

1. Introduction to FBA
2. Hands-on: linear optimisation
3. Hands-on: FBA with *COBRA* library

Toy reaction-system



Toy reaction-system

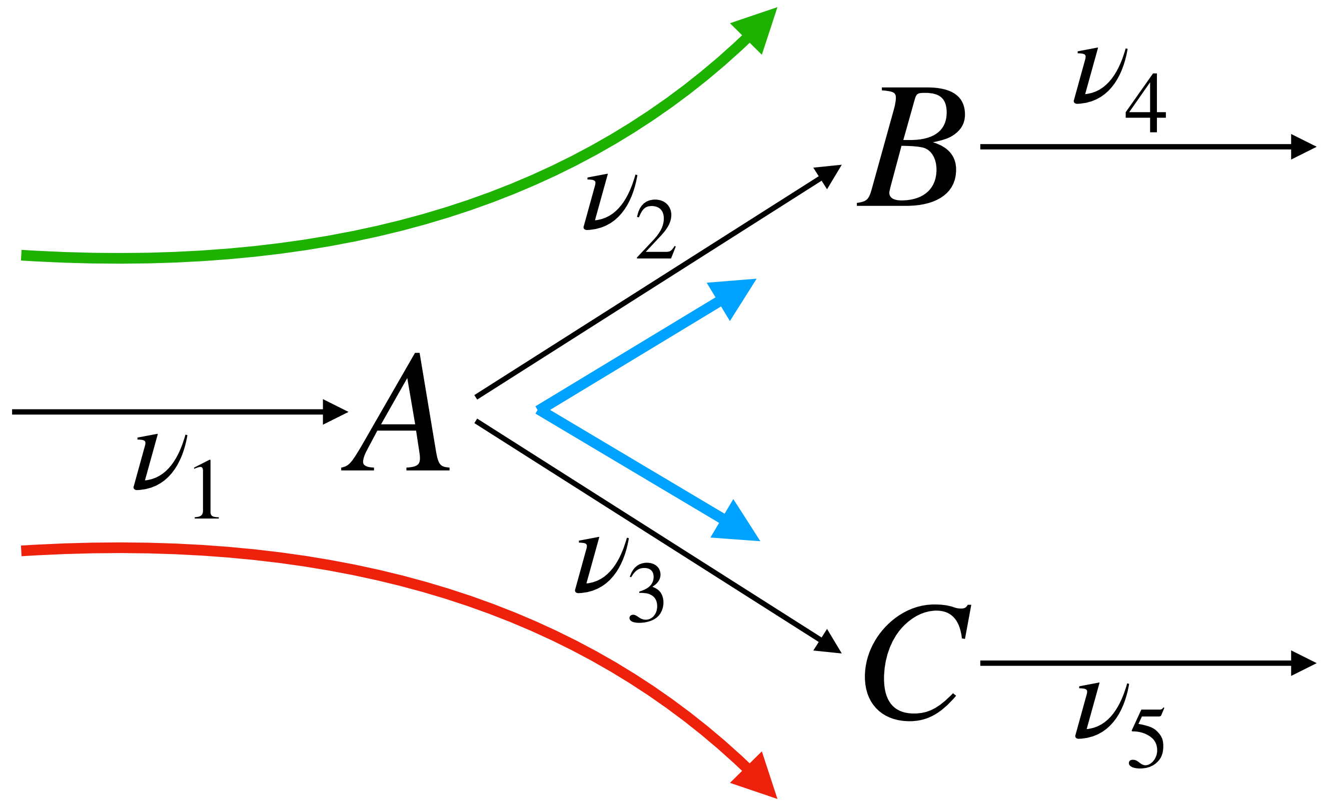


$$\frac{dA}{dt} = \nu_1 - \nu_2 - \nu_3 = \nu_1 - k_2 A - k_3 A$$

$$\frac{dB}{dt} = \nu_2 - \nu_4 = k_2 A - k_4 B$$

$$\frac{dC}{dt} = \nu_3 - \nu_5 = k_3 A - k_5 C$$

System in steady state

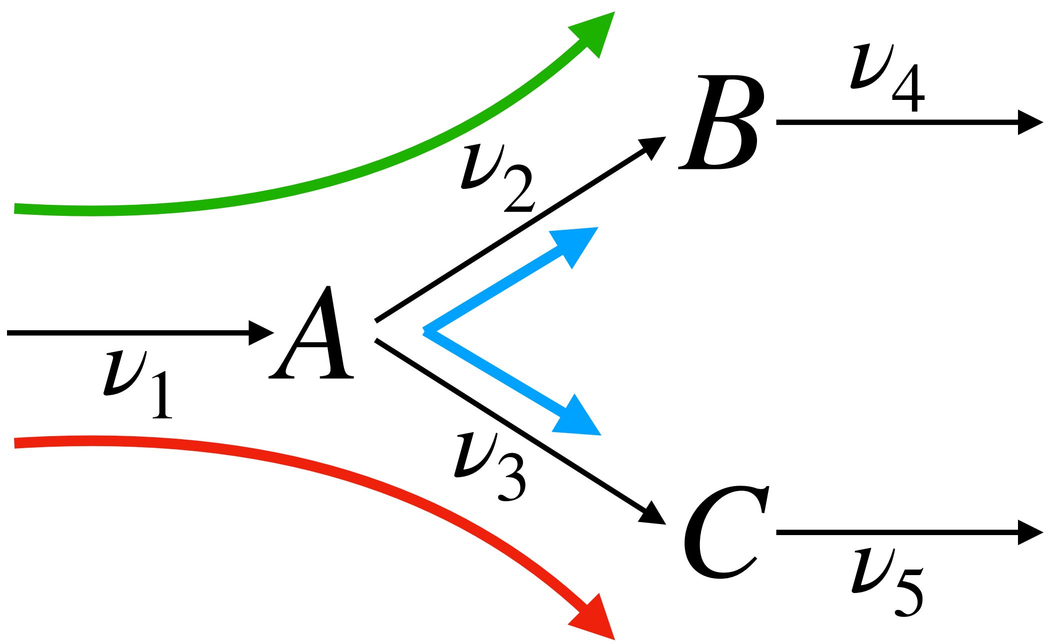


$$\frac{dA}{dt} = \nu_1 - \nu_2 - \nu_3 \boxed{= 0}$$

$$\frac{dB}{dt} = \nu_2 - \nu_4 \boxed{= 0}$$

$$\frac{dC}{dt} = \nu_3 - \nu_5 \boxed{= 0}$$

System in steady state

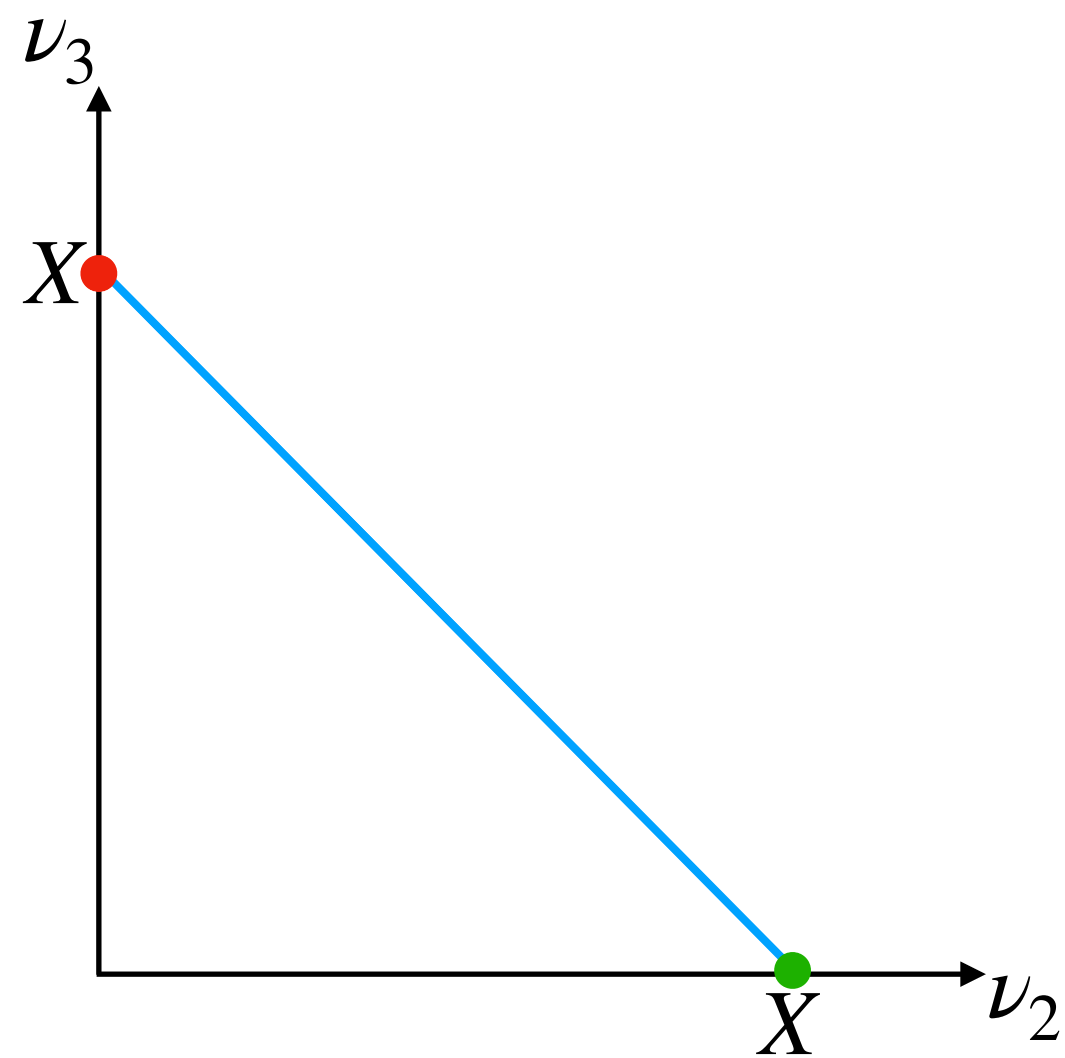


$$\frac{dA}{dt} = \nu_1 - \nu_2 - \nu_3 = 0 \rightarrow \nu_1 = \nu_2 + \nu_3$$

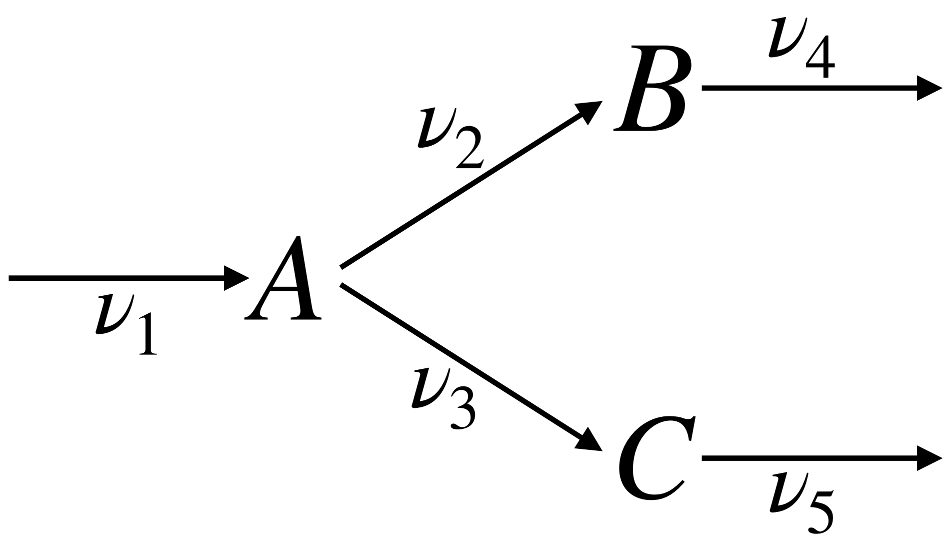
$$\frac{dB}{dt} = \nu_2 - \nu_4 = 0 \rightarrow \nu_2 = \nu_4$$

$$\frac{dC}{dt} = \nu_3 - \nu_5 = 0 \rightarrow \nu_3 = \nu_5$$

$$\nu_1 \triangleq X \rightarrow$$



Stoichiometry matrix



$$
\begin{aligned}
R_1 &: \rightarrow 1A \\
R_2 &: 1A \rightarrow 1B \\
R_3 &: 1A \rightarrow 1C \\
R_4 &: 1B \rightarrow \\
R_5 &: 1C \rightarrow
\end{aligned}
$$

$$\frac{dA}{dt} = 1\nu_1 - 1\nu_2 - 1\nu_3 = 0$$

$$\frac{dB}{dt} = 1\nu_2 - 1\nu_4 = 0$$

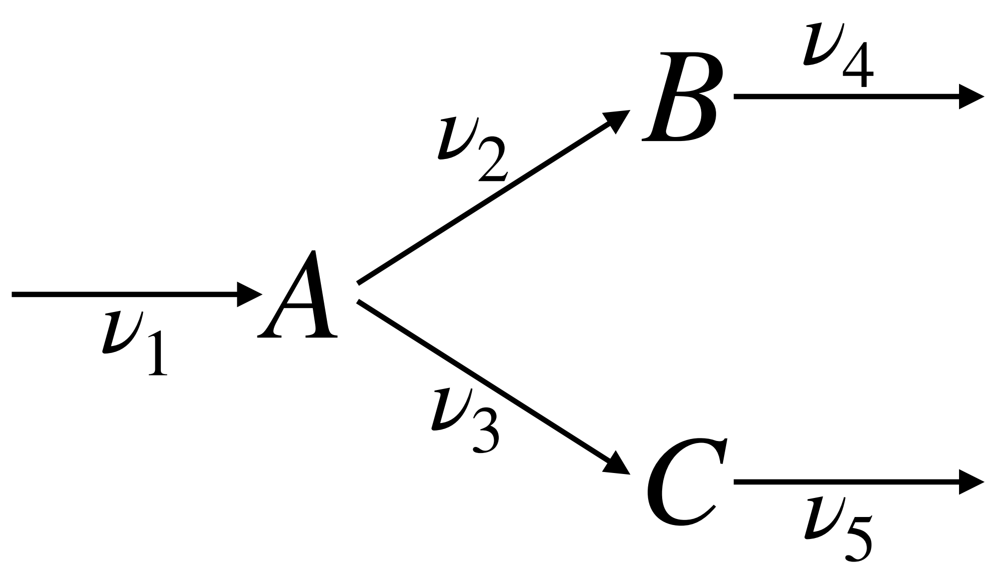
$$\frac{dC}{dt} = 1\nu_3 - 1\nu_5 = 0$$

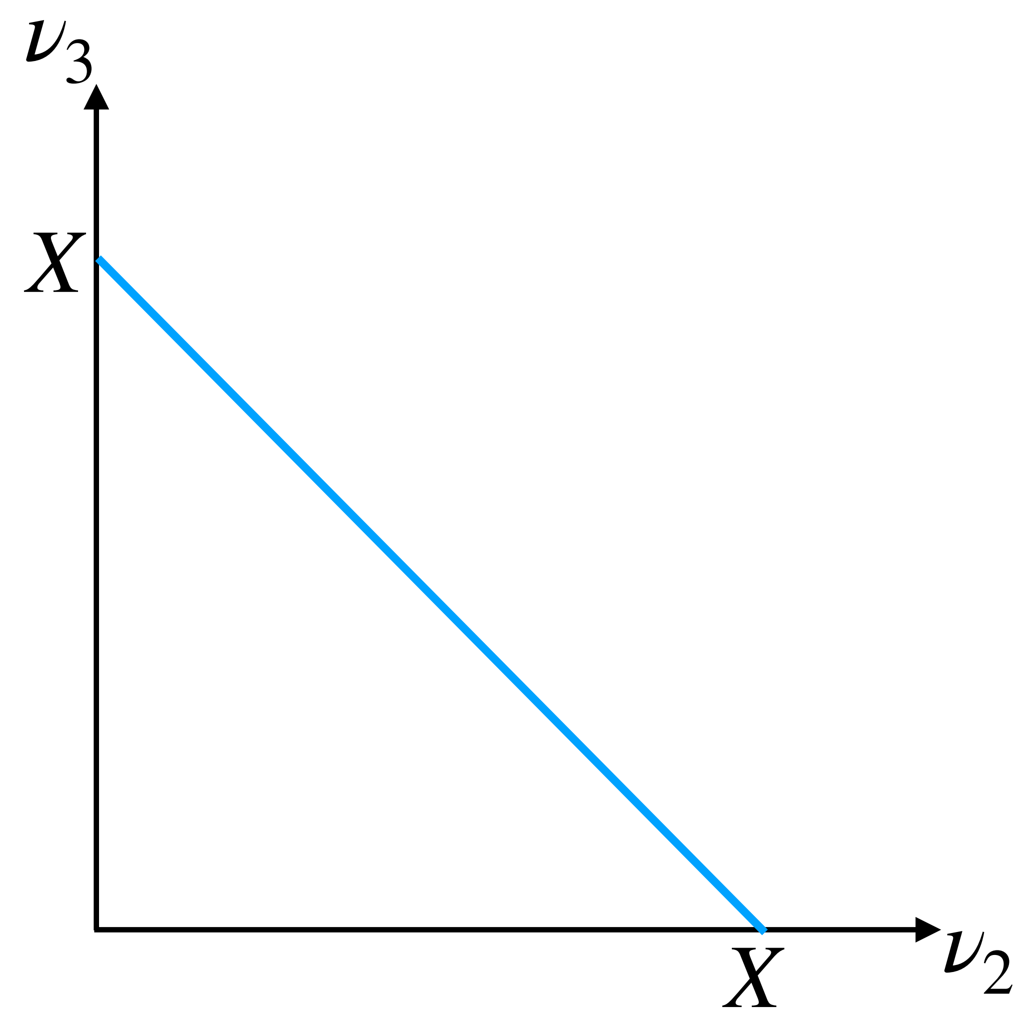
$$
\begin{array}{ccccccc}
 & \nu_1 & \nu_2 & \nu_3 & \nu_4 & \nu_5 & \\
A & 1 & -1 & -1 & 0 & 0 & = 0 \\
B & 0 & 1 & 0 & -1 & 0 & = 0 \\
C & 0 & 0 & 1 & 0 & -1 & = 0 \\
\ldots & 1 & 0 & 0 & 0 & 0 & = X
\end{array}
$$

Gaussian elimination

	ν_1	ν_2	ν_3	ν_4	ν_5	
A	1	-1	-1	0	0	$=0$
B	0	1	0	-1	0	$=0$
C	0	0	1	0	-1	$=0$
$\dots$	1	0	0	0	0	$=X$

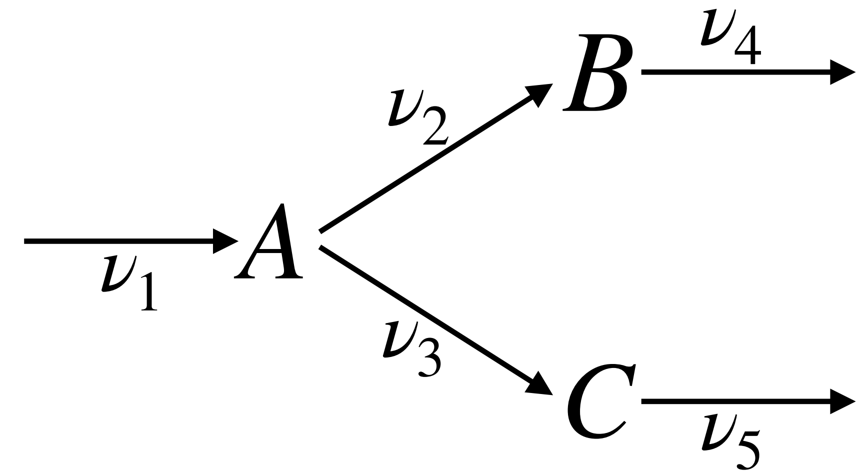
$$\nu_1 = X$$
$$\nu_4 = \nu_2$$
$$\nu_5 = \nu_3$$
$$\nu_2 = \nu_1 - \nu 3 = X - \nu_3$$





Solution space

$$
\begin{array}{cccccccc}
 & \nu_1 & \nu_2 & \nu_3 & \nu_4 & \nu_5 & \\
A & 1 & -1 & -1 & 0 & 0 & = 0 \\
B & 0 & 1 & 0 & -1 & 0 & = 0 \\
C & 0 & 0 & 1 & 0 & -1 & = 0 \\
\ldots & 1 & 0 & 0 & 0 & 0 & = X
\end{array}
$$



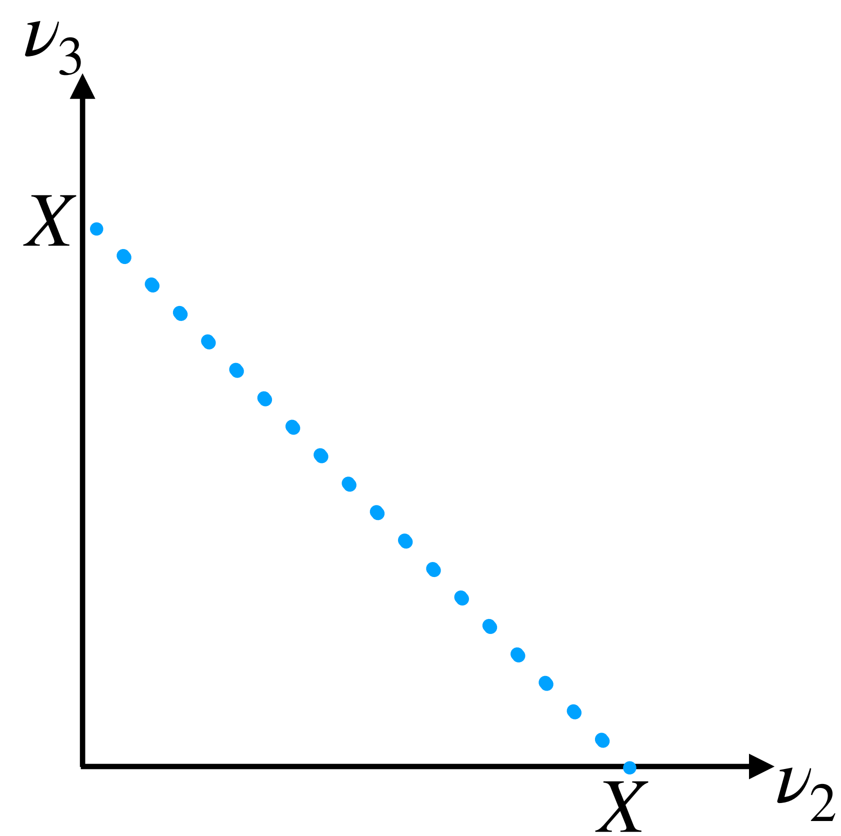
Underdetermined!

$$\nu_1 = X$$

$$\nu_4 = \nu_2$$

$$\nu_5 = \nu_3$$

$$\boxed{\nu_2 = \nu_1 - \nu 3 = X - \nu_3}$$



Solution space with inequalities

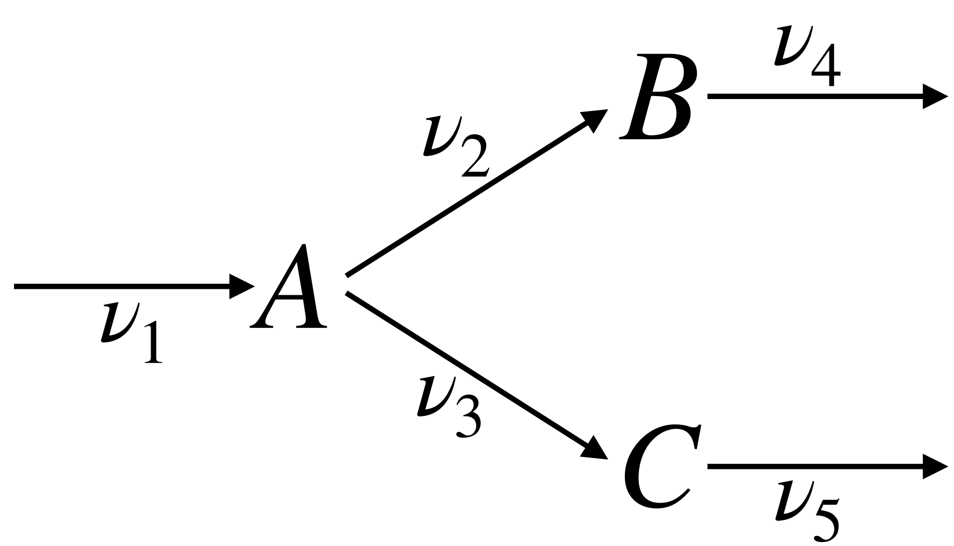
$R_1 : \rightarrow 1A$

$R_2 : 1A \rightarrow 1B$

$R_3 : 1A \rightarrow 1C$

$R_4 : 1B \rightarrow$

$R_5 : 1C \rightarrow$



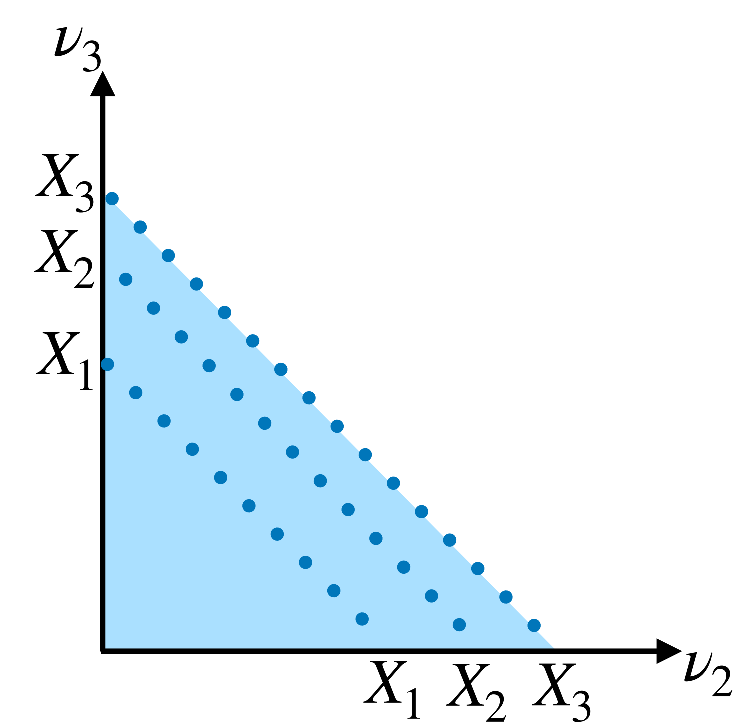
$$\frac{dA}{dt} = 1\nu_1 - 1\nu_2 - 1\nu_3 = 0$$

$$\frac{dB}{dt} = 1\nu_2 - 1\nu_4 = 0$$

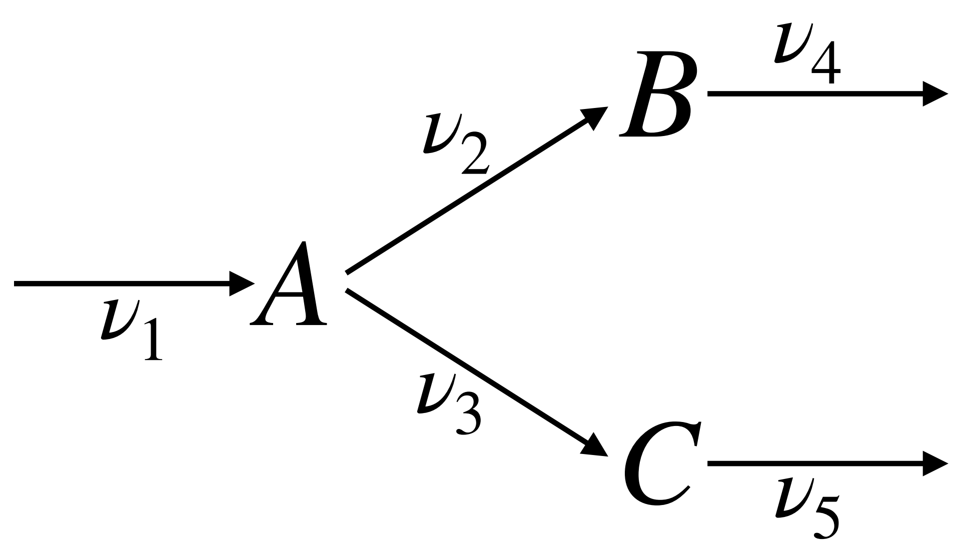
$$\frac{dC}{dt} = 1\nu_3 - 1\nu_5 = 0$$

$$\begin{array}{ccccccc}
 & \nu_1 & \nu_2 & \nu_3 & \nu_4 & \nu_5 & \\
A & 1 & -1 & -1 & 0 & 0 & = 0 \\
B & 0 & 1 & 0 & -1 & 0 & = 0 \\
C & 0 & 0 & 1 & 0 & -1 & = 0 \\
\ldots & 1 & 0 & 0 & 0 & 0 & \leq X
\end{array}$$

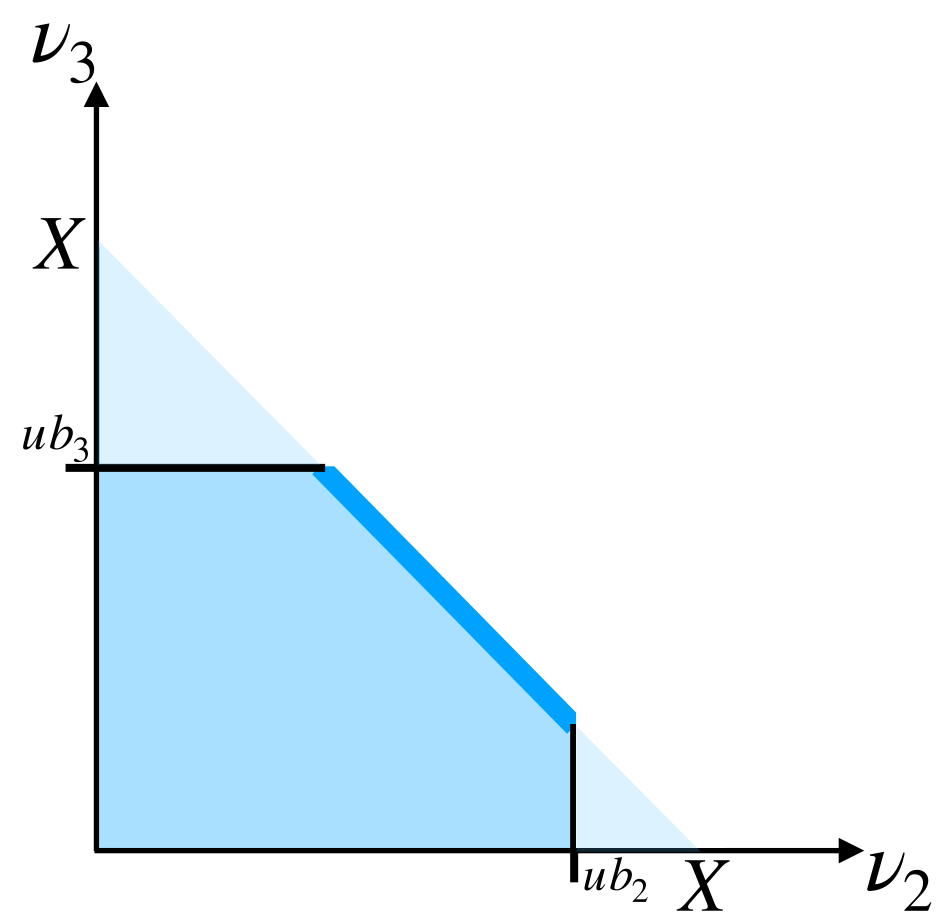
!



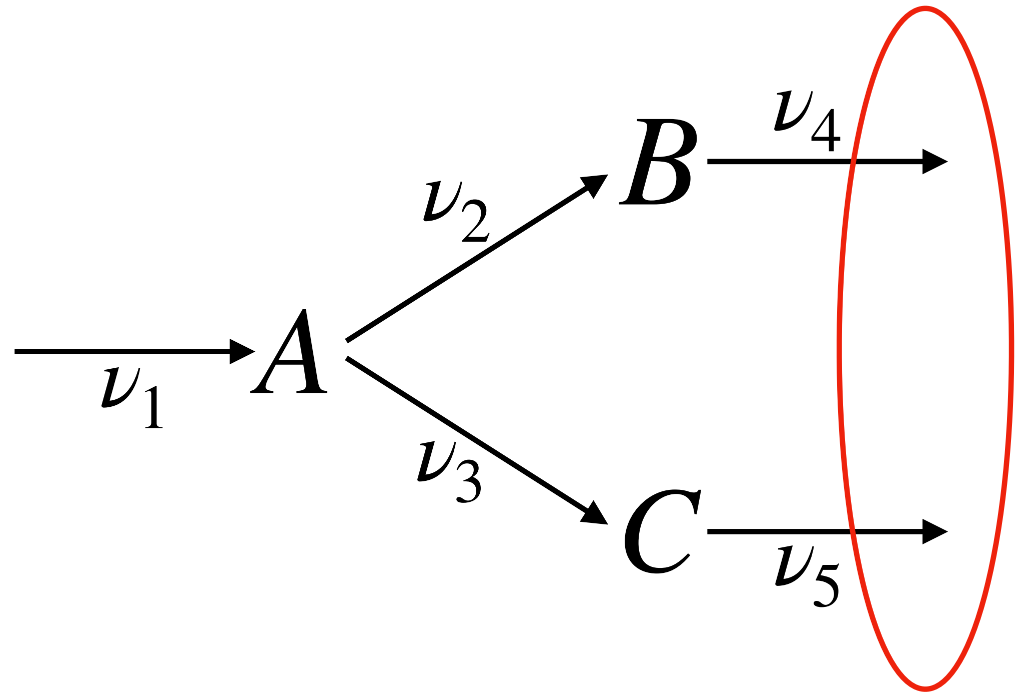
Limits to reaction-rates



	ν_1	ν_2	ν_3	ν_4	ν_5	
A	1	-1	-1	0	0	$=0$
B	0	1	0	-1	0	$=0$
C	0	0	1	0	-1	$=0$
$\ldots$	1	0	0	0	0	$\leq X$
$\ldots$	0	1	0	0	0	≥ 0
$\ldots$	0	0	1	0	0	≥ 0
$\ldots$	0	1	0	0	0	$\leq ub_2$
$\ldots$	0	0	1	0	0	$\leq ub_3$



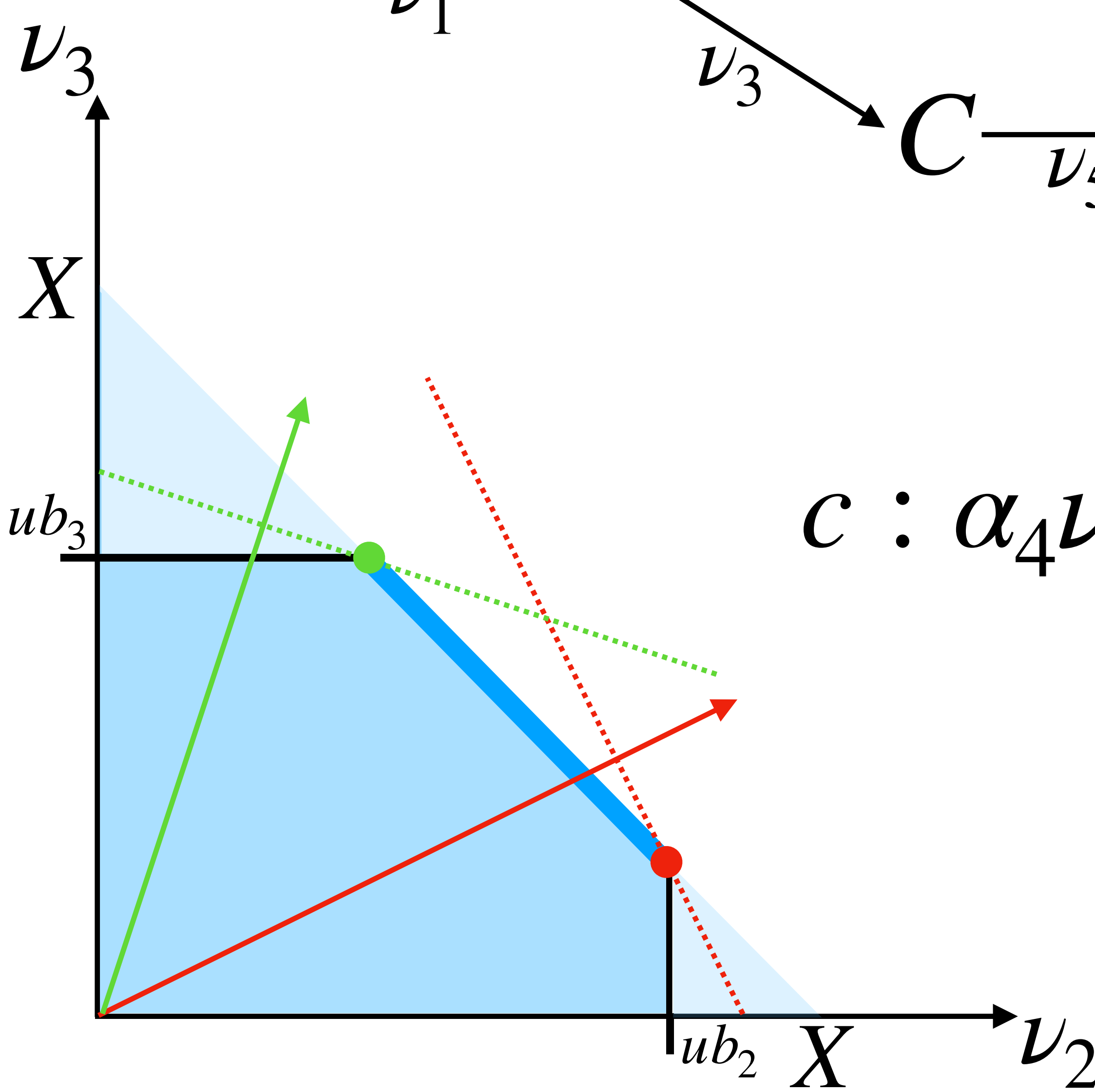
Selecting solutions



Assigning "value"
to different system outputs

System objective is defined
by assigned values

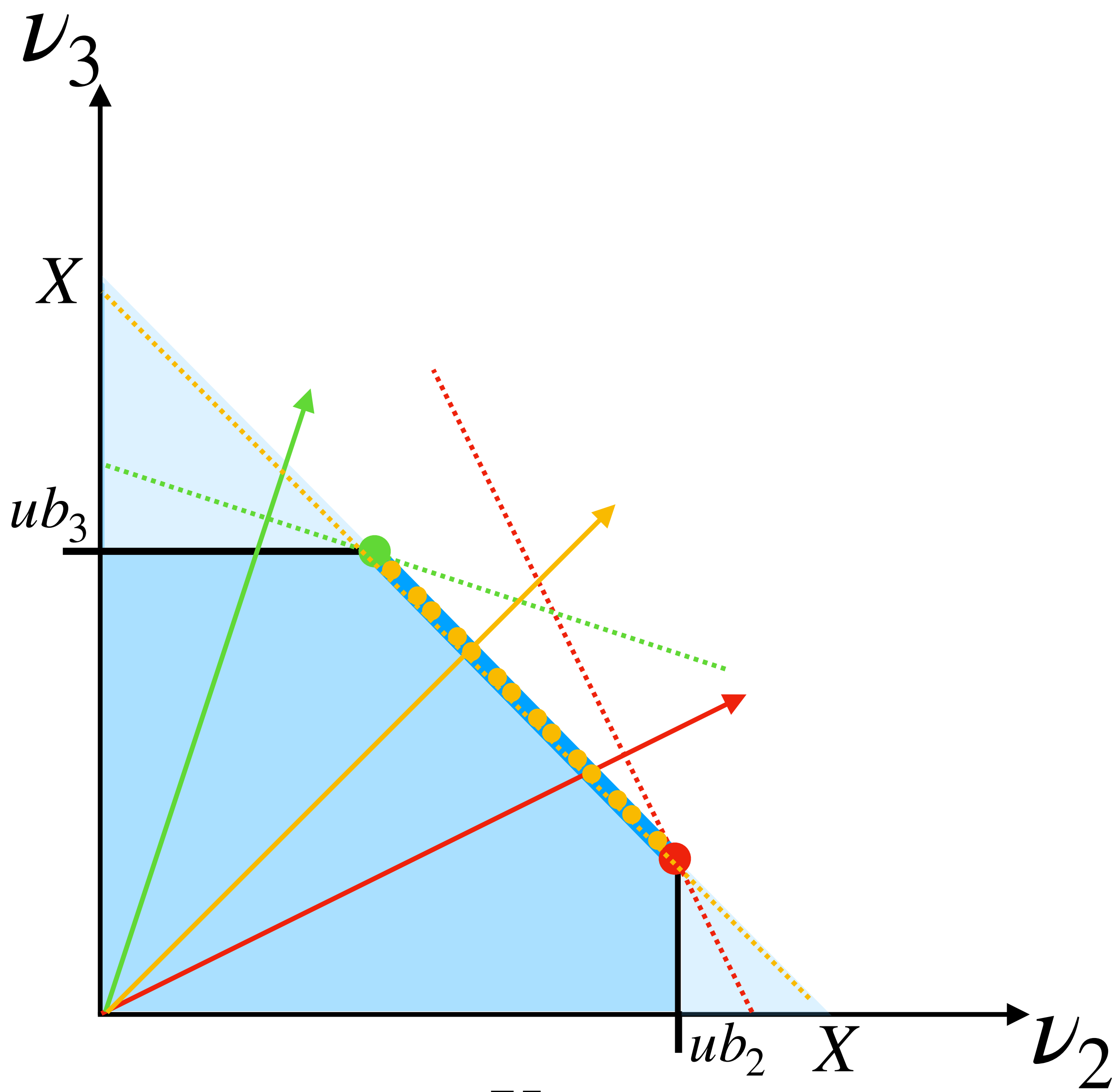
Objective function:
weighted sum of system variables



$$c : \alpha_4\nu_4 + \alpha_5\nu_5 = \alpha_2\nu_2 + \alpha_3\nu_3$$

α_2	α_3
1	3
2	1

Uniqueness of optima



	ν_1	ν_2	ν_3	ν_4	ν_5	
A	1	-1	-1	0	0	$=0$
B	0	1	0	-1	0	$=0$
C	0	0	1	0	-1	$=0$
$\dots$	1	0	0	0	0	$\leq X$
$\dots$	0	1	0	0	0	≥ 0
$\dots$	0	0	1	0	0	≥ 0
$\dots$	0	1	0	0	0	$\leq ub_2$
$\dots$	0	0	1	0	0	$\leq ub_3$
$\dots$	0	α_2	α_3	0	0	$= Z_{obj}$

Might be determined now

$$\nu_1 = X$$

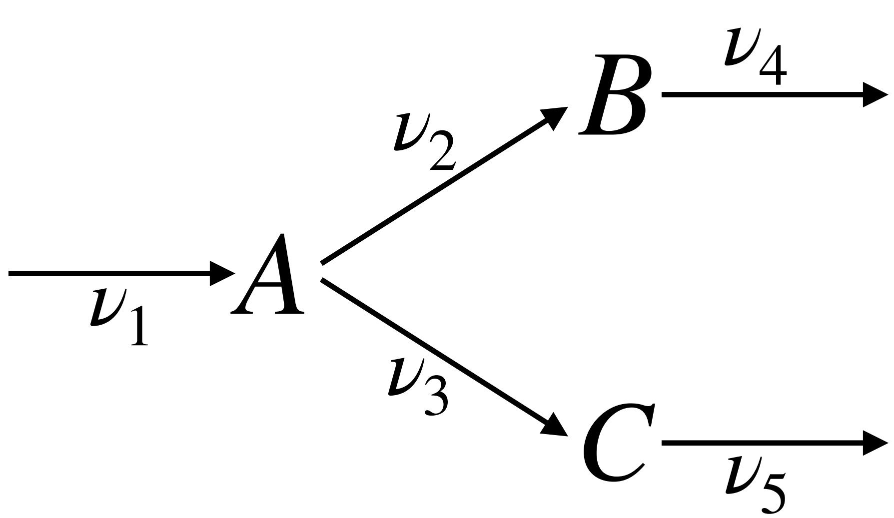
$$\nu_2 = X - \nu_3$$

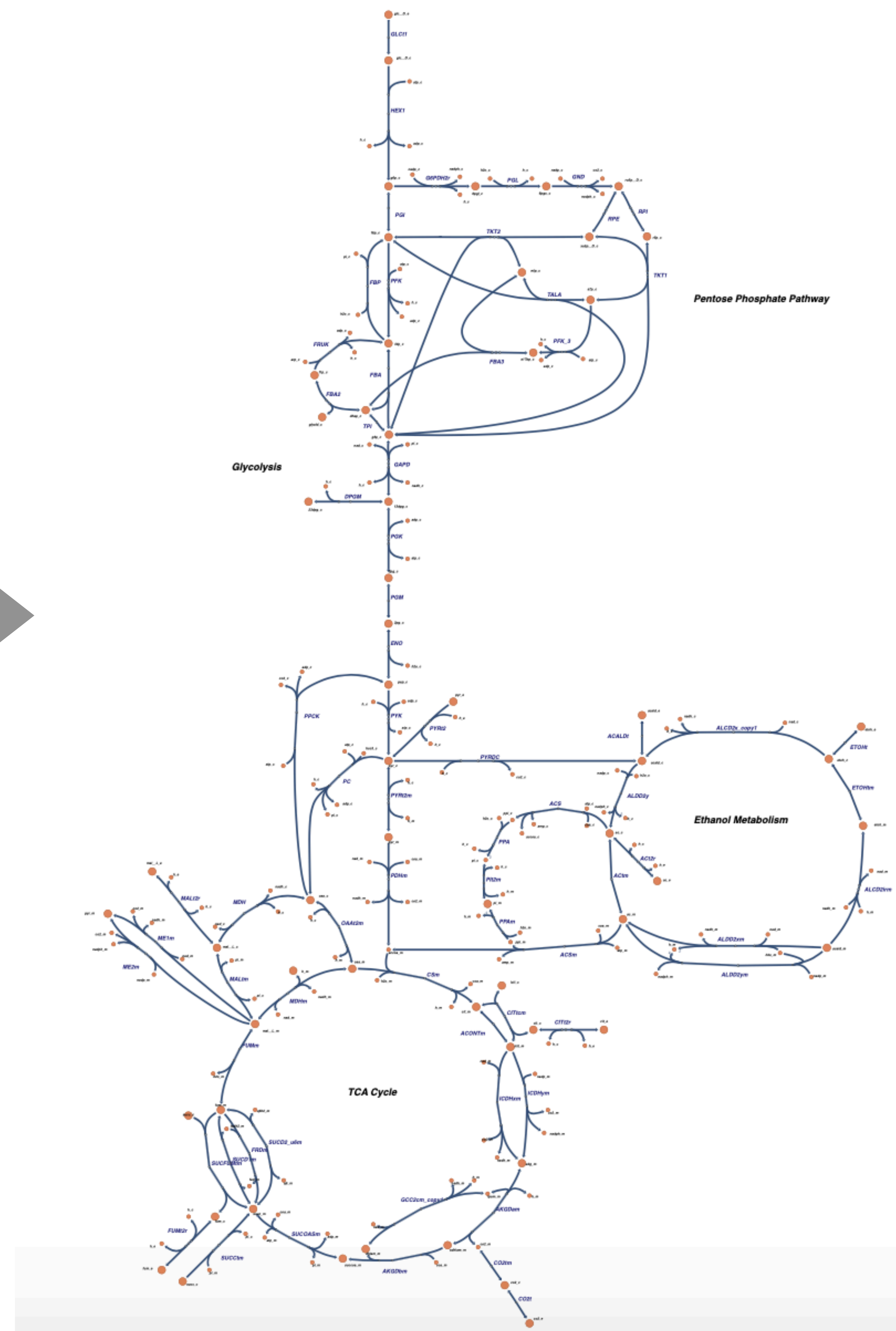
$$\alpha_2(X - \nu_3) + \alpha_3 \nu_3 = Z_{obj}$$

If $\alpha_2 \neq \alpha_3$:

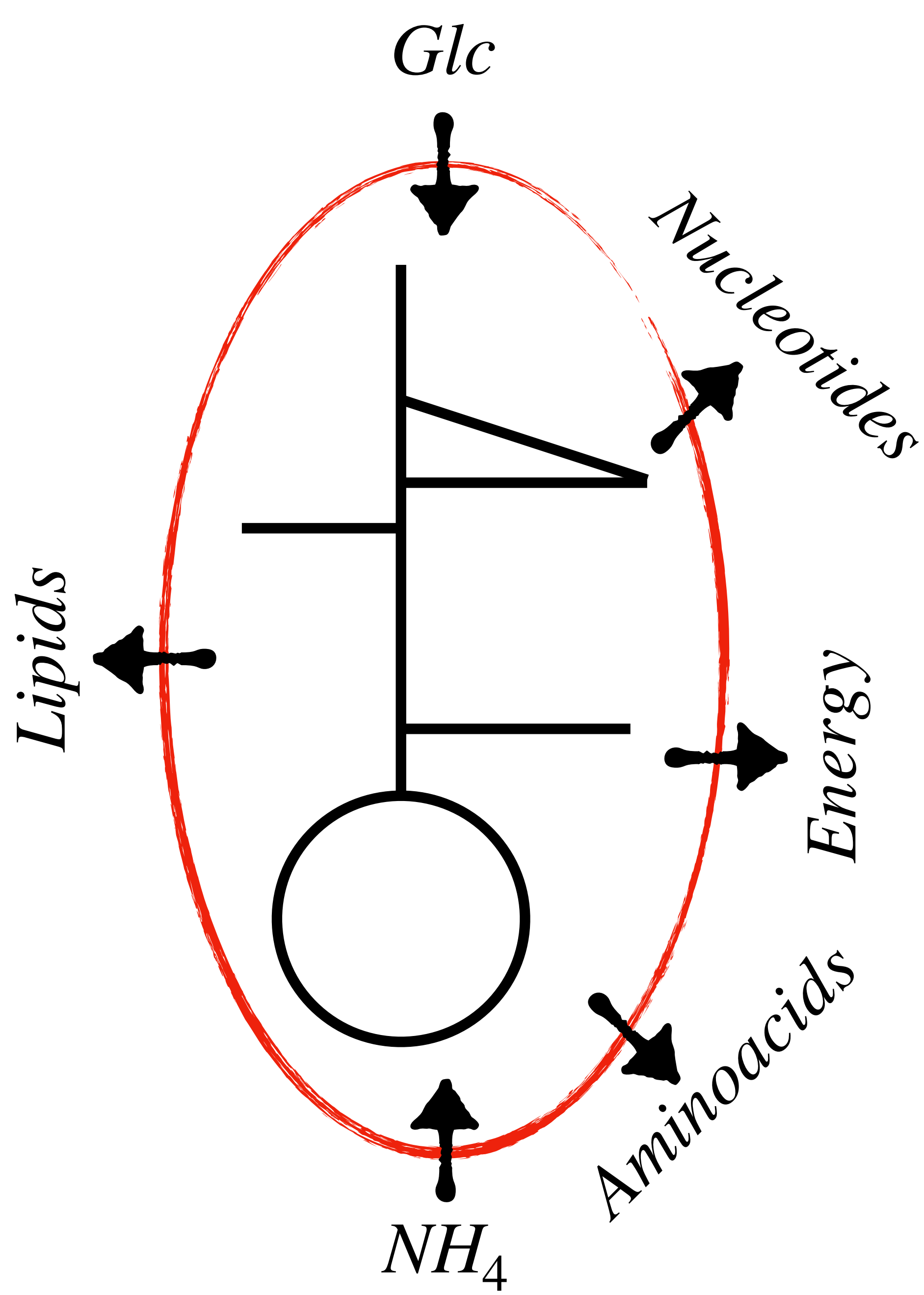
$$\nu_3 = \frac{(Z_{obj} - \alpha_2 X)}{(\alpha_3 - \alpha_2)}$$

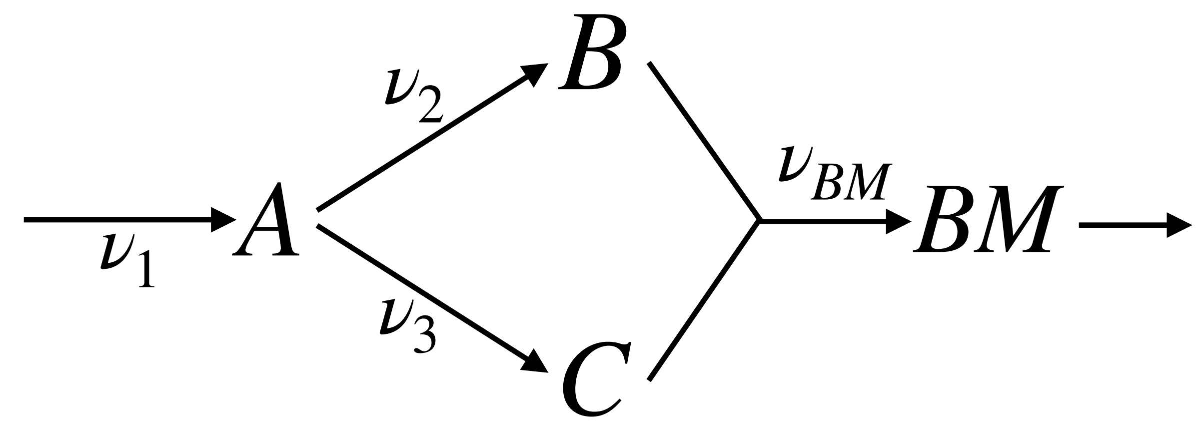
Genome-scale metabolism





Biomass-function as objective





R_{BM} :

$$\alpha_1 Energy + \alpha_2 AA + \alpha_3 Lipid + \alpha_4 Nucleotide \rightarrow$$

$$\begin{array}{ccccc}
 & \nu_1 & \nu_2 & \nu_3 & \\
A & 1 & -1 & -1 & = 0 \\
B & 0 & 1 & 0 & = 0 \\
C & 0 & 0 & 1 & = 0 \\
\dots & 1 & 0 & 0 & \leq X \\
\dots & 0 & 1 & 0 & \geq 0 \\
\dots & 0 & 0 & 1 & \geq 0 \\
\dots & 0 & 1 & 0 & \leq ub_2 \\
\dots & 0 & 0 & 1 & \leq ub_3 \\
\dots & 0 & \alpha_2 & \alpha_3 & = Z_{obj}
\end{array}$$

$$\begin{array}{cccccc}
 & \nu_1 & \nu_2 & \nu_3 & \nu_{BM} & \\
A & 1 & -1 & -1 & 0 & = 0 \\
B & 0 & 1 & 0 & -\alpha_2 & = 0 \\
C & 0 & 0 & 1 & -\alpha_3 & = 0 \\
\dots & 1 & 0 & 0 & 0 & \leq X \\
\dots & 0 & 1 & 0 & 0 & \geq 0 \\
\dots & 0 & 0 & 1 & 0 & \geq 0 \\
\dots & 0 & 1 & 0 & 0 & \leq ub_2 \\
\dots & 0 & 0 & 1 & 0 & \leq ub_3 \\
\dots & 0 & 0 & 0 & 1 & = Z_{obj}
\end{array}$$